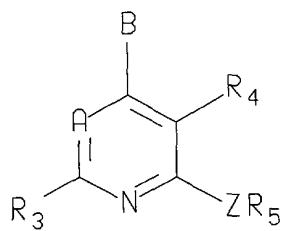
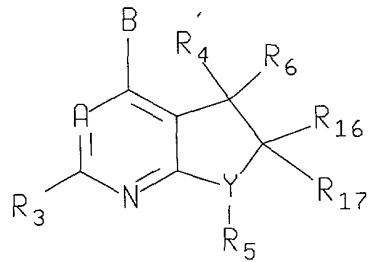


CLAIMS

1. A compound of the formula

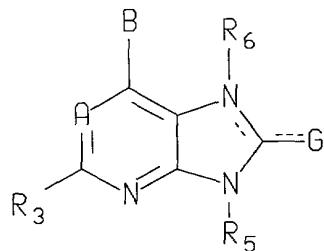


I



II

or



III

or a pharmaceutically acceptable salt thereof, wherein

5 the dashed lines represent optional double bonds, with the proviso that when the dashed line in C—G represent a double bond, then the dashed line in N(R₆)—C does not represent a double bond; and with the proviso that when the dashed line in N(R₆)—C represents a double bond, R₆ is absent in formula III and the dashed line in C—G does not represent a double bond;

10 A is -CR₇ or N;

B is -NR₁R₂, -CR₁R₂R₁₁, -C(=CR₂R₁₂)R₁, -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₂OR₁, -CHR₁OR₂, -CHR₂SR₁, -C(S)R₂, -C(O)R₂, -CHR₂NR₁R₂, -CHR₁NHR₂, -CHR₁N(CH₃)R₂, or -NR₁₂NR₁R₂;

when the dashed line in C--G represents a double bond, then G is hydrogen, oxygen, sulfur, NH, or N(C₁-C₄ alkyl);

when the dashed line in C--G does not represent a double bond, then C--G is -C(H)(NH₂), CH₂, -C(H)(methoxy), -C(H)(ethoxy), -C(H)(O(C₃-C₄ alkyl)), -C(H)(halo), -

5 C(H)(trifluoromethoxy), -C(H)(methyl), -C(H)(ethyl), -C(H)(C₃-C₄ alkyl), -C(H)(S(C₁-C₄ alkyl)), -C(C₁-C₄ alkyl)(C₁-C₄ alkyl), cyclopropyl, -C(H)(cyclopropyl), thiomethoxy, -C(H)(NH₂), -C(H)(NHCH₃), -C(H)(N(CH₃)₂), or -C(H)(trifluoromethyl);

wherein said cyclopropyl, methoxy, ethoxy, C₃-C₄ alkyl, and C₁-C₄ alkyl groups of C--G may optionally be substituted by one OH, methoxy, or trifluoromethoxy, or may optionally be substituted by from one to six fluoro atoms;

Y is CH or N;

Z is NH, O, S, -N(C₁-C₂ alkyl), -NC(O)CF₃, or -C(R₁₃R₁₄), wherein R₁₃ and R₁₄ are each, independently, hydrogen, trifluoromethyl or methyl, or one of R₁₃ and R₁₄ is cyano and the other is hydrogen or methyl, or -C(R₁₃R₁₄) is a cyclopropyl group, or Z is nitrogen or CH and forms a

15 five or six membered heterocyclic ring fused with R₅, which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR₁₂, and S(O)_m, and optionally comprises from one to three double bonds, and is optionally substituted with halo, C₁-C₄ alkyl, -O(C₁-C₄ alkyl), NH₂, NHCH₃, N(CH₃)₂, CF₃, or OCF₃, with the proviso that said ring does not contain any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and does not comprise 20 more than two oxygen or S(O)_m heterologous members;

R₁ is C(O)H, C(O)(C₁-C₆ alkyl), C(O)(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), C(O)(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C(O)(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -C(O)(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -25 -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), or -O-aryl, or -O-(C₁-C₆ alkylene)-aryl; wherein said aryl, C₄-C₈ heterocycloalkyl, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₈ cycloalkylene, and C₁-C₆ alkylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R₈ independently selected from the group consisting of C₁-C₄ alkyl, -C₃-C₈ 30 cycloalkyl, hydroxy, chloro, bromo, iodo, CF₃, -O-(C₁-C₆ alkyl), -O-(C₃-C₅ cycloalkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(R₂₄)(R₂₅), -N(R₂₄)(R₂₅), -S(C₁-C₄ alkyl), -S(C₃-C₅ cycloalkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)⁻, -SO(C₁-C₄ alkyl) and -SO₂(C₁-C₄ alkyl); and wherein the C₁-C₆ alkyl, C₁-C₆ alkylene, C₅-C₈ cycloalkyl, C₅-C₈ cycloalkylene, and C₅-C₈ heterocycloalkyl moieties of R₁ may optionally 35 independently contain from one to three double or triple bonds; and wherein the C₁-C₄ alkyl

moieties and C₁-C₆ alkyl moieties of R₈ can optionally independently be substituted with hydroxy, amino, C₁-C₄ alkyl, aryl, -CH₂-aryl, C₃-C₅ cycloalkyl, or -O-(C₁-C₄ alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocycloalkyl group of R₁ contains from 5 one to three heteromoiety selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

R₂ is hydrogen, C₁-C₁₂ alkyl, C₃-C₈ cycloalkyl, C₄-C₈ heterocycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₁-C₆ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, -(C₁-C₆ alkylene)aryl, or -(C₃-C₈ cycloalkylene)aryl; wherein each of the foregoing R₂ groups may optionally be 10 substituted with from one to three substituents independently selected from chloro, fluoro, and C₁-C₆ alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C₁-C₆ alkoxy, -OH, -O-CO-(C₁-C₆ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), -S(O)(C₁-C₆ alkyl), -S(O)₂(C₁-C₆ alkyl), S⁺(C₁-C₆ alkyl)(C₁-C₂ alkyl)I⁻, CN, and NO₂; and wherein 15 the C₁-C₁₂ alkyl, -(C₁-C₆ alkylene), -(C₅-C₈ cycloalkyl), -(C₅-C₈ cycloalkylene), and -(C₅-C₈ heterocycloalkyl) moieties of R₂ may optionally independently contain from one to three double or triple bonds; and wherein each heterocycloalkyl group of R₂ contains from one to three heteromoiety selected from oxygen, S(O)_m, nitrogen, and NR₁₂;

or when R₁ and R₂ are as in -NHCHR₁R₂, -OCHR₁R₂, -SCHR₁R₂, -CHR₁R₂ or -NR₁R₂, R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally contain one or 20 two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO₂(C₁-C₄ alkyl), 25 wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, 30 -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ alkyl, C₃-C₅ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O-(C₃-C₅ cycloalkyl), -O-(C₁-C₄ alkylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), -CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ alkylene)-35 OR₂₄, -(C₁-C₄ alkylene)Cl, -(C₁-C₄ alkylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -C=NOR₂₄, -NHN₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHN₂₄R₂₅, and -

COOR₂₄, wherein the alkyl and alkylene groups of R₄ may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R₁₀ independently selected from hydroxy, amino, -NHCOCH₃, -NHCOCH₂Cl, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₂ alkyl), -COO(C₁-C₄ alkyl), -COOH, -CO(C₁-C₄ alkyl), C₁-C₆ alkoxy, C₁-C₃ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R₅ is aryl or heteroaryl and is substituted with from one to four substituents R₂₇ independently selected from halo, C₁-C₁₀ alkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkyl), -(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, nitro, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, -NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, -CO(NOR₂₂)R₂₃, -CO₂R₂₆, -C=N(OR₂₂)R₂₃, and -S(O)_mR₂₃; wherein said C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ alkylene), (C₃-C₈ cycloalkyl), (C₃-C₈ cycloalkylene), and (C₄-C₈ heterocycloalkyl) groups can be optionally substituted with from one to three substituents independently selected from C₁-C₄ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, hydroxy, C₁-C₆ alkoxy, nitro halo, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, and -S(O)_mR₂₃; and wherein two adjacent substituents of the R₅ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R⁵, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₆)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇ can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -NHSO₂(C₃-C₈ cycloalkyl), -NHSO₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSO₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the alkyl, and alkylene groups of R₅ may independently optionally contain one double or triple bond;

R₆ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

or, wherein the compound is a compound of formula II, R₆ and R₄ can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous

ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl, wherein said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

5 R₇ is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C₁-C₂ alkyl), -O(cyclopropyl), -COO(C₁-C₂ alkyl), -COO(C₃-C₈ cycloalkyl), -OCF₃, CF₃, -CH₂OH, or CH₂OCH₃;

R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl;

10 R₁₆ and R₁₇ are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R₁₆ and R₁₇ are not both methoxy or ethoxy;

15 or R₁₆ and R₁₇ together form an oxo (=O) group;

or R₁₆ and R₁₇ are connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing from one to three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ alkyl or C₃-C₆ cycloalkyl, wherein

20 said C₁-C₄ alkyl substituent may optionally contain one double or triple bond;

R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄ alkylene)(C₃-C₈ cycloalkyl);

25 R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

30 R₂₄ and R₂₅ are independently at each occurrence selected from hydrogen, -C₁-C₄ alkyl, C₁-C₄ haloalkyl, especially CF₃, -CHF₂, CF₂CF₃, or CH₂CF₃, -(C₁-C₄ alkylene)OH, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-O-(C₃-C₅ cycloalkyl), C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -C₄-C₈ heterocycloalkyl, -(C₁-C₄ alkylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), aryl, and -(C₁-C₄ alkylene)(aryl), wherein the -C₄-C₈ heterocycloalkyl groups can each independently optionally be substituted with aryl, CH₂-aryl, or C₁-C₄ alkyl, and can optionally contain one or two double or triple bonds; or, when R₂₄ and R₂₅ are as NR₂₄R₂₅, -C(O)NR₂₄R₂₅, -(C₁-C₄ alkylene)NR₂₄R₂₅, or -NHCONR₂₄R₂₅, then NR₂₄R₂₅ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from S(O)_m, oxygen, nitrogen, and NR₁₂, and optionally containing from one to three double bonds;

R_{26} is independently at each occurrence selected from C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_8 cycloalkyl, $-(C_1$ - C_4 alkylene) $(C_3$ - C_8 cycloalkyl), $-(C_3$ - C_8 cycloalkylene) $(C_3$ - C_8 cycloalkyl), aryl, and $-(C_1$ - C_4 alkylene)(aryl); and

wherein each m is independently zero, one, or two,

5 with the proviso that heterocycloalkyl groups of the compound of formula I, II, or III do not comprise any $-S-S-$, $-S-O-$, $-N-S-$, or $-O-O-$ bonds, and do not comprise more than two oxygen or $S(O)_m$ heterologous members.

2. A compound according to claim 1, wherein R_4 is $-NHCH_2CF_3$, $-CONHNH_2$, $-CONHNHCH_3$, $-OCF_3$, fluoro, $-OCHF_2$, $-OCH_2(C_3$ - C_5 cycloalkyl), $-O-(C_3$ - C_5 cycloalkyl), $10 -SCH_2(C_3$ - C_5 cycloalkyl), $-S(C_3$ - C_5 cycloalkyl), $-OCH_3$, $-CH_3$, $-CH_2CH_3$, chloro, bromo, $-CF_3$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCF_3$, $-SCH_3$, $-S(O)CH_3$, $-S(O)_2CH_3$, $-C(O)CH_3$, $-NR_{24}R_{25}$, $-NO_2$, $-CH(OH)CH_3$ or $-CN$.

3. A compound according to claim 1, wherein R_4 is $-C(O)NR_{24}R_{25}$ or $-C(O)NHNR_{24}R_{25}$.

15 4. A compound according to claim 1, wherein R_4 is $-(C_1$ - C_4 alkylene) $NR_{24}R_{25}$.

5. A compound according to claim 1, wherein R_4 is $-COOCH_3$ or $-COOCH_2CH_3$.

6. A compound of formula I according to claim 1, wherein Z is O ; B is $-NHCHR_1R_2$, wherein R_1 is $-C(O)H$, $-C(O)(C_1$ - C_6 alkyl), or $-C_1$ - C_6 alkyl, wherein said C_1 - C_6 alkyl is optionally substituted with from one to six fluoro atoms or one or two R_8 independently selected from $-C_1$ - C_4 alkyl, hydroxy and $-O-(C_1$ - C_6 alkyl), and wherein R_2 is $-C_1$ - C_{12} alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C_1 - C_6 alkyl; R_5 is phenyl, pyridyl or pyrimidyl, substituted with two or three R_{27} groups selected from halo, $-(C_1$ - C_4 haloalkyl), $-C(O)R_{24}$, $-OR_{25}$, $-C(O)NR_{24}R_{25}$, and C_1 - C_{10} alkyl which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C_1 - C_6 alkoxy, and $-NR_{24}R_{25}$; and R_4 is $-C(O)NR_{24}R_{25}$.

7. A compound of formula I according to claim 1, wherein Z is O ; B is $-NHCHR_1R_2$, wherein R_1 of $-NHCHR_1R_2$ is $-C(O)H$, $-C(O)(C_1$ - C_6 alkyl), or $-C_1$ - C_6 alkyl, wherein said C_1 - C_6 alkyl is optionally substituted with from one to six fluoro atoms or one or two R_8 independently selected from $-C_1$ - C_4 alkyl, hydroxy and $-O-(C_1$ - C_6 alkyl), and wherein R_2 of $-NHCHR_1R_2$ is $-C_1$ - C_{12} alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one three substituents selected from fluoro and C_1 - C_6 alkyl; R_5 is phenyl, pyridyl or pyrimidyl, substituted with two or three R_{27} groups selected from halo, $-(C_1$ - C_4 haloalkyl), $-C(O)R_{24}$, $-OR_{25}$, $-C(O)NR_{24}R_{25}$, and C_1 - C_{10} alkyl which is optionally substituted with one to three substituents, preferably one substituent, selected from hydroxy, C_1 - C_6 alkoxy, and $-NR_{24}R_{25}$; and R_4 is $-NR_1R_2$, wherein R_1 of $-NR_1R_2$ is C_1 - C_6 alkyl,

C₃-C₈ cycloalkyl, or -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), and R₂ of -NR₁R₂ is C₁-C₁₂ alkyl optionally containing from one to three double or triple bonds and optionally substituted with from one to three fluoro atoms.

8. A compound according to claim 1 selected from:

5 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6,N-dimethyl-nicotinamide;

10 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-methoxymethyl-propylamino)-6-methyl-nicotinamide;

 2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6-methyl-nicotinamide;

15 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinamide;

 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-N-dimethyl-nicotinamide;

20 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2R-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1S,2S-1-ethyl-2-methoxy-propylamino)-6,N-dimethyl-nicotinamide;

 2-(4-bromo-2-methoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

25 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzamide;

 2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(1-methylsulfanylmethyl-propylamino)-nicotinic acid methyl ester;

 2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-hydroxymethyl-propylamino)-6-methyl-nicotinic acid methyl ester;

30 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinonitrile;

 2-(4-chloro-2-trifluoromethoxy-phenoxy)-4-(1-ethyl-propylamino)-6-methyl-nicotinic acid methyl ester; and

 2-(4-chloro-2,6-dimethyl-phenoxy)-6-methyl-4-(tetrahydro-furan-3-ylamino)-nicotinic acid methyl ester;

35 and pharmaceutically acceptable salts thereof.

9. A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with 5 premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal 10 diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate 15 antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune 20 dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the 25 Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

30 10. A method for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder or condition selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias, including social phobia, agoraphobia, 35 and specific phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as

depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; 5 spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies or 10 addictions, including dependencies or addictions to alcohol, cocaine, heroin, benzodiazapines, or other drugs; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, including cerebral ischemia, for example cerebral hippocampal ischemia; excitotoxic neuronal 15 damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions, including porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human-animal interaction stress in dogs; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and 20 Syndrome X in a mammal or bird, comprising administering to a subject in need of said treatment an amount of a compound according to claim 1, that is effective in treating such disorder or condition.

11. A method of treating a condition comprising administering a compound of claim 1 in an amount effective to treat said condition, wherein said condition is selected from 25 the group consisting of:

- a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF 30 antagonist; and
- c) emesis.

12. The method of claim 11 wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

13. The method of claim 12, wherein said second compound is selected from the 35 group consisting of tachykinin antagonists, agonists for GABA brain receptors, metalonergic

compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding.

14. The method of claim 11 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the 5 group consisting of selective serotonin reuptake inhibitors, tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the 10 above-recited compounds.

15. The method of claim 11 wherein said condition is emesis, further comprising administering a second compound for treating emesis.

16. The method of claim 15 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA 15 agonists, and substance P inhibitors.

17. A pharmaceutical composition for treating a condition comprising a compound of claim 1 in an amount effective to treat said condition and a pharmaceutically acceptable carrier, wherein said condition is selected from the group consisting of:

- 20 a) abnormal circadian rhythm;
- b) depression, further wherein a second compound for treating depression is administered, said second compound for treating depression having an onset of action that is delayed with respect to that of said CRF antagonist; and
- c) emesis.

25 18. A pharmaceutical composition according to claim 17, wherein the condition is abnormal circadian rhythm, and the compound is combined with a second compound useful for treating a sleep disorder.

19. A pharmaceutical composition according to claim 18, wherein said second compound is selected from the group consisting of tachykinin antagonists, agonists for GABA 30 brain receptors, metalonergic compounds, GABA brain receptor agonists, 5HT₂ receptor antagonists, and D4 receptor binding.

20. A pharmaceutical composition according to claim 17 wherein said condition is depression, and wherein said second compound having delayed action for treating depression is selected from the group consisting of selective serotonin reuptake inhibitors, 35 tricyclic antidepressants, norepinephrine uptake inhibitors, lithium, bupropion, sertraline, fluoxetine, trazodone, and a tricyclic antidepressant selected from the group consisting of

imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, clomipramine, maprotiline, and carbamazepine, and pharmaceutically acceptable salts and esters of the above-recited compounds.

21. A pharmaceutical composition according to claim 17 wherein said condition is
5 emesis, further comprising administering a second compound for treating emesis.

22. A pharmaceutical composition according to claim 21 wherein said second compound for treating emesis is selected from the group consisting of tachykinin antagonists, 5HT3 antagonists, GABA agonists, and substance P inhibitors.

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